

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000244 A1

(51) International Patent Classification⁷: A61K 31/17,
A61P 31/00, 43/00

(21) International Application Number: PCT/EP02/06538

(22) International Filing Date: 13 June 2002 (13.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
101 29 704.1 22 June 2001 (22.06.2001) DE

(71) Applicant: AVENTIS PHARMA DEUTSCHLAND
GMBH [DE/DE]; Brüningstrasse 50, 65929 Frankfurt
(DE).

(72) Inventors: GERLACH, Uwe; Im Heideck 30, 65795 Hat-
tersheim (DE). WIRTH, Klaus; Robert-Schumann-Ring
104, 65830 Kriftel (DE). ENGLERT, Heinrich, Chris-
tian; Stormstrasse 13, 65719 Hofheim (DE). GÖGELEIN,
Heinz; Zum Eiskeller 7, 60259 Frankfurt am Main (DE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN,
YU, ZA, ZM, ZW.

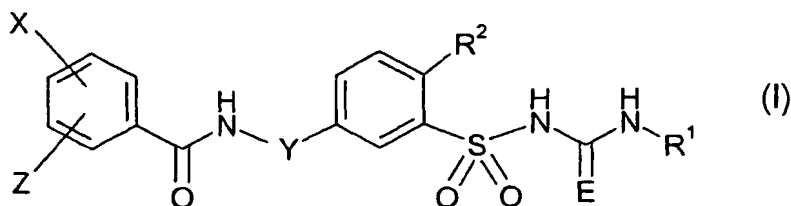
(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: BENZENESULFONYL(THIO)UREAS FOR THE TREATMENT OF SEPTIC SHOCK AND SIRS



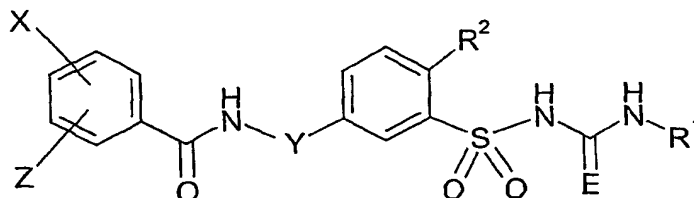
(57) Abstract: The present invention relates to the use of substituted benzenesulfonylureas and benzenesulfonylthioureas of the formula (I), in which R¹, R², E, X, Y and Z have the meanings given in the claims, for treating pathological changes in blood pressure associated with the disease patterns of septic shock and generalized inflammatory syndrome, and to their use for producing medicaments for this purpose.

WO 03/000244 A1

BENZENESULFONYL(THIO)UREAS FOR THE TREATMENT OF SEPTIC SHOCK AND SIRS

The present invention relates to the use of substituted benzenesulfonylureas and benzenesulfonylthioureas of the formula I

5



in which R¹, R², E, X, Y and Z have the meanings given below, for treating pathological changes in blood pressure associated with the disease patterns of septic shock and generalized inflammatory syndrome, and to their use for producing medicaments for this purpose.

Compounds of the formula I are disclosed, for example, in US-A-5574069 (EP-A-612724) and US-A-5652268 (EP-A-727416) whose content is incorporated herein by reference. These documents report that compounds of the formula I selectively inhibit ATP-sensitive potassium channels in the heart and exert a direct antiarrhythmic effect by influencing the duration of the action potential of the heart as a result of the direct effect on the electrical properties of heart muscle cells. Due to this property, the compounds of the formula I are suitable, for example, for treating ventricular fibrillation and other cardiac rhythm disturbances. WO-A-00/15204 reports that compounds of the formula I can also be employed in the treatment and prophylaxis of dysfunctions of the autonomic nervous system. It has now been found, surprisingly, that the compounds of the formula I are outstandingly suitable for use in the treatment of septic shock of a very wide variety of origins and of the generalized inflammatory syndrome, specifically for the treatment of the pathological changes in blood pressure which are associated with septic shock and the generalized inflammatory syndrome.

The disease pattern of sepsis is associated with a general inflammatory reaction and pronounced impairment of hemodynamics, respiration and metabolism which arise, for example, as the result of a massive infiltration of pathogenic bacteria, or their toxins, into the blood circulation. The observation that noxae other than an infection
5 are also able to give rise to very similar disease states led to the introduction of the *superordinate concept of the generalized inflammatory syndrome (SIRS, systemic inflammatory response syndrome)*.

Sepsis and the generalized inflammatory syndrome (SIRS) lead, in particular, to
10 characteristic hemodynamic changes which acutely endanger the blood supply to the body. Sepsis is accompanied by a life-threatening reduction in the systemic blood pressure (generalized circulatory failure; septic shock). Paradoxically, however, the blood pressure (pulmonary arterial pressure) in the lesser circulation, i.e. the pulmonary circulation, can increase in this connection, with this increase possibly
15 constituting a dangerous stress for the right ventricle which further aggravates the overall hemodynamic situation. The right-heart insufficiency which is thereby induced can determine, and dramatically aggravate, the entire cardiovascular situation.

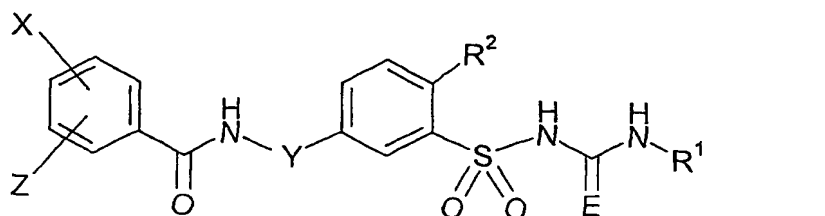
The therapeutic objective when treating the cardiovascular problems which are
20 associated with sepsis or which occur in the generalized inflammatory syndrome state would be to at least increase the reduced peripheral blood pressure without (further) increasing the pulmonary arterial pressure, however, it would be ideal if it were possible to lower the pulmonary arterial pressure in addition to increasing the peripheral blood pressure. Vasoconstrictive substances which come into
25 consideration for treating the cardiovascular problems exhibit a favorable effect in the systemic circulation by increasing the peripheral (systemic) blood pressure, however, a simultaneously effected vasoconstriction in the pulmonary vascular system would lead to a (further) increase in the pulmonary arterial pressure and thereby reduce the output from the right ventricle. A pulmonary vasoconstriction can consequently lead
30 to a dangerous reduction in the cardiac minute output and to circulatory collapse.

It would consequently be desirable to have available medicaments which bring about peripheral vasoconstriction without at the same time having a vasoconstrictive effect in the pulmonary vascular system or, even more advantageously, medicaments which even have a vasodilatory effect in the lung. The vasoactive substances which increase both the systemic arterial pressure and the pulmonary arterial pressure, and which have been investigated in animal experiments relating to septic shock or human sepsis, include the benzenesulfonylurea glibenclamide and NO synthase inhibitors (NO = nitric oxide) such as L-NMA (N-methylarginine) or L-NAME (N-nitroarginine methyl ester). However, leaving aside other effects and side-effects, these substances would not, as has been explained, be suitable for treating septic shock because of their hemodynamic effect profile, i.e. the fact that they cause vasoconstriction in both the systemic circulation and in the pulmonary circulation. Further comments in this regard are found in the literature such as, for example, J. Wanstall, Gen. Pharmacol. 1996, 27, 599; M. Dumas et al., Brit. J. Pharmacol. 1997, 120, 405; S. Barman, Am. J. Physiol. 1998, 275, L64; J. Avontuur et al., Crit. Care Med. 1998, 26, 660; R. Weingartner et al., Braz. J. Med. Biol. Res. 1999, 32, 1505; D. Landry et al., J. Clin. Invest. 1992, 89, 2071.

It has now been found that, surprisingly, in the disease pattern of septic shock and of the generalized inflammatory syndrome (SIRS) the compounds of formula I increase the peripheral (systemic) blood pressure and, at the same time, lower the pulmonary arterial pressure and consequently possess the desired property profile for treating the pathological changes in blood pressure and the cardiovascular problems which are associated with this disease pattern.

25

The present invention consequently relates to the use of benzenesulfonyl(thio)ureas of the formula I



in which

R¹ is hydrogen, (C₁-C₈)-alkyl, (C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkyl-(C₁-C₄)-alkyl- or
 5 fluoro-(C₁-C₈)-alkyl-;

R² is (C₁-C₆)-alkoxy, (C₃-C₈)-cycloalkyloxy, (C₃-C₈)-cycloalkyl-(C₁-C₄)-alkoxy-, (C₁-
 C₆)-alkoxy-(C₁-C₄)-alkoxy- or (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy-(C₁-C₄)-alkoxy-;

E is oxygen or sulfur;

Y is a hydrocarbon residue of the formula -(CR³)_n-, in which the residues R³, all
 10 independently of each other, are hydrogen or (C₁-C₂)-alkyl, and n is 1, 2, 3 or 4;

X is hydrogen, halogen or (C₁-C₆)-alkyl;

Z is halogen, (C₁-C₄)-alkyl, fluoro-(C₁-C₄)-alkyl-, (C₁-C₄)-alkoxy or fluoro-(C₁-C₄)-
 alkoxy-;

in all their stereoisomeric forms and mixtures thereof in all ratios, and/or their

15 physiologically tolerated salts, in the treatment of septic shock or the generalized
 inflammatory syndrome (SIRS), and to their use for producing a medicament for
 treating septic shock or the generalized inflammatory syndrome (SIRS), in particular
 their use for treating pathological changes in blood pressure in septic shock or in the
 generalized inflammatory syndrome (SIRS) state, and to their use for producing a
 20 medicament for treating pathological changes in blood pressure in septic shock or in
 the generalized inflammatory syndrome (SIRS) state. The term "treating pathological
 changes in blood pressure" also encompasses the use of the compounds of the
 formula I and/or their physiologically tolerated salts for preventing or obviating or
 alleviating pathological changes in blood pressure in septic shock or in the
 25 generalized inflammatory syndrome (SIRS) state.

Alkyl is straight-chain or branched saturated hydrocarbon residues. This also applies
 when the alkyl residue is substituted, as in fluoroalkyl residues for example, or occurs

as a substituent on another residue, for example in alkoxy residues or fluoroalkoxy residues. Examples of straight-chain and branched alkyl residues are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl and n-octyl.

5

Examples of cycloalkyl residues are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Cycloalkyl residues can additionally carry one or more, for example, 1, 2, 3 or 4, identical or different (C₁-C₄)-alkyl residues or (C₁-C₄)-fluoroalkyl residues, for example methyl groups or trifluoromethyl groups. Examples of

10 cycloalkyl-alkyl- residues are cyclopropylmethyl-, cyclobutylmethyl-, cyclopentylmethyl-, cyclohexylmethyl-, cycloheptylmethyl-, cyclooctylmethyl-, 1-cyclopropylethyl-, 2-cyclopropylethyl-, 1-cyclopentylethyl-, 2-cyclopentylethyl-, 1-cyclohexylethyl-, 2-cyclohexylethyl-, 3-cyclopropylpropyl-, 3-cyclopentylpropyl-, 3-cyclohexylpropyl- and 4-cyclopropylbutyl-.

15

Examples of the alkoxy (= alkyloxy) residue which is bonded via an oxygen atom are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxo, neopentoxo and isohexoxy. Examples of the cycloalkyloxy residue are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

20

Fluoroalkyl is an alkyl residue in which one or more hydrogen atoms of an alkyl residue, which is defined as above, have been replaced with fluorine atoms. One or more fluorine atoms, for example 1, 2, 3, 4, 5, 6 or 7, can be present in a fluoroalkyl residue. As a maximum, all the hydrogen atoms can be replaced, that is

25 perfluorosubstitution can be present. Examples of fluoroalkyl are fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl. Fluoroalkoxy is an alkoxy residue which is defined as above and in which, as explained, one or more hydrogen atoms, for example one, two, three or four hydrogen atoms, have been replaced with fluorine atoms. Examples of fluoroalkoxy are trifluoromethoxy and
30 2,2,2-trifluoroethoxy.

The above definitions and explanations also apply, independently of each other, to all alkyl groups in the alkoxy-alkoxy- and alkoxy-alkoxy-alkoxy- residues which residues are bonded via an oxygen atom. In the divalent alkyl groups which are contained in these groups, the two free bonds by which these groups are bonded to the

5 neighboring groups can be present in any positions, for example in the 1,1 position of an alkyl residue, in the 1,2 position, in the 1,3 position or in the 1,4 position.

Examples of such divalent residues are methylene, 1,2-ethylene, 1,2-propylene, 1,3-propylene, 1,4-butylene and 2,2-dimethyl-1,3-propylene. A preferred divalent residue of this nature is 1,2-ethylene. Examples of alkoxy-alkoxy- residues are

10 methoxy-methoxy-, 2-methoxy-ethoxy-, 3-methoxy-propoxy-, 4-methoxy-butoxy-, 6-methoxy-hexoxy-, 2-ethoxy-ethoxy-, 2-ethoxy-2-methyl-ethoxy-, 3-ethoxy-propoxy-, 2-propoxy-ethoxy-, 2-isobutoxy-ethoxy- and 2-tert-butoxy-ethoxy-. Examples of alkoxy-alkoxy-alkoxy- residues are (2-methoxy-ethoxy)-methoxy-, 2-(2-methoxy-ethoxy)-ethoxy-, 2-(2-isopropoxy-ethoxy)-ethoxy-, 2-(2-n-butoxy-ethoxy)-ethoxy-, 3-
15 (2-methoxy-ethoxy)-propoxy- and 2-(2-methoxy-2-methyl-ethoxy)-2-methyl-ethoxy-.

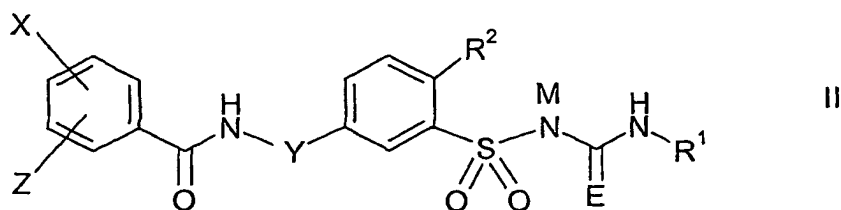
Examples of halogen are fluorine, chlorine, bromine and iodine, in particular fluorine and chlorine.

20 The present invention encompasses all stereoisomeric forms of the compounds of the formula I. Centers of asymmetry which are present in the compounds of the formula I, for example in the Y group or in alkyl groups, can all, independently of each other, exhibit the S configuration or the R configuration. All possible enantiomers and diastereomers, as well as mixtures of two or more stereoisomeric
25 forms, for example mixtures of enantiomers and/or diastereomers, in all ratios, are comprised by the invention. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. Diastereomers are a subject-matter of the invention both in pure form and in the form
30 of mixtures of two or more diastereomers in all ratios. The invention also encompasses meso compounds. When a cis/trans isomerism is present, both the cis form and the trans form and mixtures of these forms in all ratios are a subject of the

invention. If desired, individual stereoisomers can be prepared by fractionating a mixture using customary methods, for example chromatography or crystallization, or by using stereochemically homogeneous starting substances in the synthesis. Where appropriate, a derivatization can be carried out before stereoisomers are separated.

- 5 A stereoisomeric mixture can be separated at the level of the compounds of the formula I or at the level of an intermediate during the course of the synthesis. The invention also encompasses all tautomeric forms of the compounds of the formula I.

Physiologically tolerated salts of the compounds of the formula I are, in particular,
10 pharmaceutically utilizable salts or nontoxic salts. They can contain inorganic or organic salt components (see Remington's Pharmaceutical Sciences, A. R. Gennaro (Editor), Mack Publishing Co., Easton PA, 17th edition, 1985, page 1418). These salts can be prepared, for example, from compounds of the formula I using suitable inorganic or organic bases, for example using basic alkali metal or alkaline earth
15 metal compounds such as sodium hydroxide or potassium hydroxide, or using ammonia or organic amino compounds or ammonium hydroxides. In general, reactions of compounds of the formula I with bases for the purpose of preparing the salts are carried out in accordance with customary procedures in a solvent or diluent, for example in an alcohol such as methanol. Because of their physiological and
20 chemical stability, advantageous salts are in many cases sodium, potassium, magnesium or calcium salts or ammonium salts, in particular sodium salts. Formation of a salt on the sulfonyl group-substituted nitrogen atom of the (thio)urea group leads to compounds of the formula II



in which R¹, R², E, X, Y and Z have the abovementioned meanings and the cation M is, for example, an alkali metal ion or one equivalent of an alkaline earth metal ion,

for example the sodium, potassium, magnesium or calcium ion, or is the unsubstituted ammonium ion or an ammonium ion having one or more organic residues. An ammonium ion standing for M can, for example, also be the cation which is obtained, by protonation, from an amino acid, in particular a basic amino acid such as lysine or arginine.

The present invention also encompasses solvates of compounds of the formula I and their physiologically tolerated salts, for example hydrates or adducts with alcohols, and also derivatives of the compounds of the formula I and prodrugs and active metabolites.

In the formula I, R^1 is preferably hydrogen, (C_1-C_8) -alkyl, (C_3-C_8) -cycloalkyl or (C_1-C_8) -fluoroalkyl-, particularly preferably hydrogen or (C_1-C_6) -alkyl, very particularly preferably hydrogen or (C_1-C_4) -alkyl, especially preferably (C_1-C_4) -alkyl, in particular methyl.

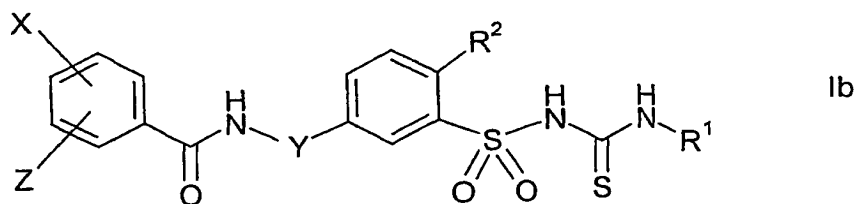
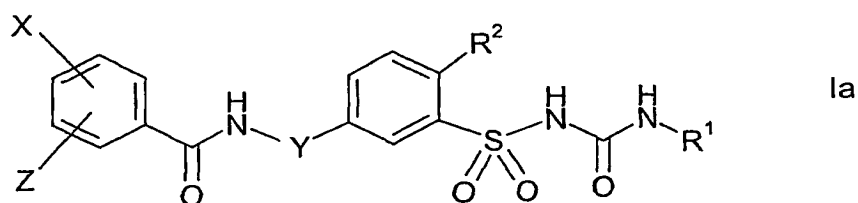
If R^2 is (C_1-C_6) -alkoxy in the formula I, the residue is then preferably (C_1-C_4) -alkoxy, in particular methoxy or ethoxy, especially methoxy. If R^2 is (C_1-C_6) -alkoxy- (C_1-C_4) -alkoxy- in the formula I, the residue is then preferably (C_1-C_4) -alkoxy- (C_1-C_4) -alkoxy-, in particular 2- $((C_1-C_4)$ -alkoxy)-ethoxy-, especially 2-methoxy-ethoxy-. If R^2 is (C_1-C_6) -alkoxy- (C_1-C_4) -alkoxy- (C_1-C_4) -alkoxy- in the formula I, the residue is then preferably (C_1-C_4) -alkoxy- (C_1-C_4) -alkoxy- (C_1-C_4) -alkoxy-, in particular 2-(2- $((C_1-C_4)$ -alkoxy)-ethoxy)-ethoxy-, especially 2-(2-methoxy-ethoxy)-ethoxy-. A group of preferred residues R^2 is formed by the residues (C_1-C_6) -alkoxy, (C_1-C_6) -alkoxy- (C_1-C_4) -alkoxy- and (C_1-C_6) -alkoxy- (C_1-C_4) -alkoxy- (C_1-C_4) -alkoxy-, in particular the residues (C_1-C_6) -alkoxy and (C_1-C_6) -alkoxy- (C_1-C_4) -alkoxy-, especially the residues methoxy and 2-methoxy-ethoxy-, very especially the residue 2-methoxy-ethoxy-.

The residues R^3 are preferably, independently of each other, hydrogen or methyl, particularly preferably hydrogen. n is preferably 2 or 3, particularly preferably 2. The group Y preferably contains up to four carbon atoms. Particularly preferably, Y is the group $-(CH_2)_n-$ in which n is 2 or 3, or is the group $-CHR^3-CH_2-$ in which R^3 is methyl

or ethyl and the group $-\text{CHR}^3-$ is bonded to the NH group. Very particularly preferably, Y is the group $-\text{CH}_2-\text{CH}_2-$.

X is preferably hydrogen, halogen or (C_1-C_4) -alkyl, particularly preferably halogen, for example fluorine, chlorine, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, in particular fluorine or chlorine, especially chlorine. Z is preferably halogen, (C_1-C_4) -alkoxy or (C_1-C_4) -alkyl, particularly preferably (C_1-C_4) -alkoxy, for example methoxy or ethoxy, especially methoxy. The residues X and Z can be located in all positions of the phenyl residue to which they are bonded. Preferably, X is bonded in the 5 position and Z in the 2 position of the phenyl residue, in each case with reference to the group $\text{C}(=\text{O})-\text{NH}$ in the 1 position.

If the group E in the compounds of the formula I to be used according to the invention is oxygen, then the ureas of the formula Ia are present, while if E is sulfur, then the thioureas of the formula Ib are present. E is preferably sulfur.



Compounds of the formula I which are preferred for the use according to the invention are compounds in which one or more of the residues have preferred meanings, with all combinations of preferred meanings being a subject of the present invention.

Thus, for example, preference is given to using compounds of the formula I in which R^1 is hydrogen, (C₁-C₈)-alkyl, (C₃-C₈)-cycloalkyl or fluoro-(C₁-C₈)-alkyl-;

R^2 is (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy- or (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy-

5 (C₁-C₄)-alkoxy-;

E is oxygen or sulfur;

Y is a hydrocarbon residue of the formula $-(CR^3_2)_n-$, in which the residues R^3 , all independently of each other, are hydrogen or (C₁-C₂)-alkyl, and n is 1, 2, 3 or 4;

X is hydrogen, halogen or (C₁-C₄)-alkyl;

10 Z is halogen, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy;

in all their stereoisomeric forms and mixtures thereof in all ratios, and/or their physiologically tolerated salts.

Particular preference is given to using compounds of the formula I in which

15 R^1 is hydrogen or (C₁-C₆)-alkyl;

R^2 is (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy- or (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy-(C₁-C₄)-alkoxy-;

E is oxygen or sulfur;

Y is a hydrocarbon residue of the formula $-(CR^3_2)_n-$, in which the residues R^3 , all

20 independently of each other, are hydrogen or (C₁-C₂)-alkyl, and n is 1, 2, 3 or 4;

X is hydrogen, halogen or (C₁-C₄)-alkyl;

Z is halogen, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy;

in all their stereoisomeric forms and mixtures thereof in all ratios, and/or their physiologically tolerated salts.

25

Very particular preference is given to using compounds of the formula I in which

R^1 is hydrogen or (C₁-C₆)-alkyl;

R^2 is methoxy or 2-methoxy-ethoxy-;

E is oxygen or sulfur;

30 Y is a hydrocarbon residue of the formula $-(CR^3_2)_n-$, in which the residues R^3 , all independently of each other, are hydrogen or methyl, and n is 2 or 3;

X is hydrogen, halogen or (C₁-C₃)-alkyl;

Z is halogen, (C₁-C₃)-alkyl or (C₁-C₃)-alkoxy;

in all their stereoisomeric forms and mixtures thereof in all ratios, and/or their physiologically tolerated salts.

5 Especial preference is given to using compounds of the formula I in which

R¹ is (C₁-C₄)-alkyl;

R² is methoxy or 2-methoxy-ethoxy-;

E is oxygen or sulfur;

Y is the hydrocarbon residue of the formula -(CR³₂)_n-, in which the residues R³ all are

10 hydrogen, and n is 2;

X is chlorine, fluorine or (C₁-C₃)-alkyl;

Z is chlorine, fluorine, (C₁-C₃)-alkyl or (C₁-C₃)-alkoxy;

in all their stereoisomeric forms and mixtures thereof in all ratios, and/or their physiologically tolerated salts.

15

In addition to this, preference is given, on the one hand, to using compounds of the formula I in which

R¹ is methyl;

R² is methoxy;

20 E is sulfur;

Y is the divalent residue -CH₂-CH₂-;

X is chlorine;

Z is methoxy;

and/or their physiologically tolerated salts,

25 and, on the other hand, to using compounds of the formula I in which

R¹ is methyl;

R² is 2-methoxy-ethoxy-;

E is sulfur;

Y is the divalent residue -CH₂-CH₂-;

30 X is chlorine;

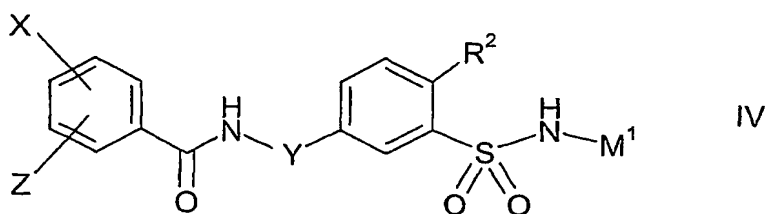
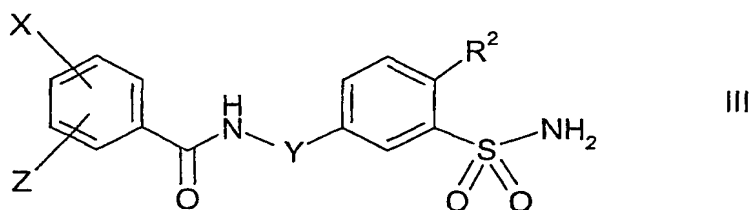
Z is methoxy;

and/or their physiologically tolerated salts.

Examples of compounds of the formula I which can be used according to the invention are 1-(5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)-phenylsulfonyl)-3-methylthiourea and its physiologically tolerated salts, for example the sodium salt, and 1-(5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-methoxy-phenylsulfonyl)-3-methylthiourea and its physiologically tolerated salts, for example the sodium salt. These two compounds can also be designated, for example, as 5-chloro-2-methoxy-N-(2-(3-methylaminothiocarbonylaminosulfonyl-4-(2-methoxyethoxy)-phenyl)ethyl)benzamide and 5-chloro-2-methoxy-N-(2-(3-methylaminothiocarbonylaminosulfonyl-4-methoxyphenyl)ethyl)benzamide.

The compounds of the formula I to be used according to the invention can be prepared, for example, by means of the following processes.

- (a) Aromatic sulfonamides of the formula III, or their salts of the formula IV, can be reacted with R^1 -substituted isocyanates of the formula V to give substituted benzenesulfonylureas of the formula Ia.



Cations M^1 which are suitable for use in the salts of the formula IV are alkali metal ions or alkaline earth metal ions, such as sodium ions or potassium ions, or ammonium ions such as, for example, tetraalkylammonium ions. Instead of the R^1 -substituted isocyanates of the formula V, also R^1 -substituted carbamic acid esters, R^1 -substituted carbamoyl halides or R^1 -substituted ureas can be used in an equivalent manner.

(b) Benzenesulfonylureas of the formula Ia which are unsubstituted at the terminal nitrogen atom of the urea group and in which R^1 is hydrogen, can be prepared by reacting aromatic benzenesulfonamides of the formula III, or their salts of the formula IV, with trialkylsilyl isocyanates, such as trimethylsilyl isocyanate, or with silicon tetrakisocyanate, and hydrolyzing the silicon-substituted benzenesulfonylureas which are initially formed. Furthermore, compounds of the formula Ia in which R^1 is hydrogen can be obtained from benzenesulfonamides of the formula III, or their salts of the formula IV, by reacting them with cyanogen halides and hydrolyzing the N-cyanosulfonamides, which are formed initially, with mineral acids at temperatures of from about 0°C to about 100°C.

(c) Benzenesulfonylureas of the formula Ia can be prepared from aromatic benzenesulfonamides of the formula III, or their salts of the formula IV, and R^1 -substituted trichloroacetamides of the formula VI in the presence of a base in an inert solvent, in accordance with Synthesis 1987, 734, at temperatures of from about 25°C to about 150°C.



VI

Examples of suitable bases are alkali metal or alkaline earth metal hydroxides, hydrides, amides or alcoholates, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium hydride, potassium hydride, calcium hydride, sodium amide, potassium amide, sodium methoxide, sodium ethoxide, potassium methoxide or potassium ethoxide. Suitable inert solvents are ethers, such as tetrahydrofuran,

dioxane or ethylene glycol dimethyl ether (DME), ketones, such as acetone or butanone, nitriles, such as acetonitrile, nitro compounds, such as nitromethane, esters, such as ethyl acetate, amides, such as dimethylformamide (DMF) or N-methylpyrrolidone (NMP), hexamethylphosphoric triamide, sulfoxides such as dimethyl sulfoxide (DMSO), sulfones, such as sulfolane, and hydrocarbons, such as benzene, toluene and xylenes. Mixtures of these solvents with one another are also suitable.

(d) Benzenesulfonylthioureas of the formula Ib can be prepared from

benzenesulfonamides of the formula III, or their salts of the formula IV, and R¹-substituted isothiocyanates of the formula VII.

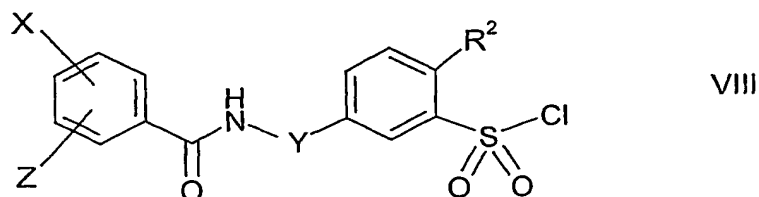


(e) Benzenesulfonylthioureas of the formula Ib which are unsubstituted at the terminal nitrogen atom of the thiourea group and in which R¹ is hydrogen, can be prepared by reacting aromatic benzenesulfonamides of the formula III, or their salts of the formula IV, with trialkylsilyl isothiocyanates, such as trimethylsilyl isothiocyanate, or with silicon tetraisothiocyanate, and hydrolyzing the silicon-substituted benzenesulfonylthioureas which are formed initially. It is furthermore possible, in order to prepare compounds of the formula Ib in which R¹ is hydrogen, to react aromatic benzenesulfonamides of the formula III, or their salts of the formula IV, with benzoyl isothiocyanate and then react the intermediary benzoyl-substituted benzenesulfonylthioureas with aqueous mineral acids. Similar processes are described in J. Med. Chem. 1992, 35, 1137.

(f) Substituted benzenesulfonylureas of the formula Ia can be prepared from benzenesulfonylthioureas of the formula Ib by means of transformation reactions. The preparation of a benzenesulfonylurea of the formula Ia by desulfurization, i.e. the replacement of the sulfur atom in the thiourea moiety of the respective benzenesulfonylthiourea with an oxygen atom, can be performed, for example, with the aid of oxides or salts of heavy metals or by using oxidizing agents such as

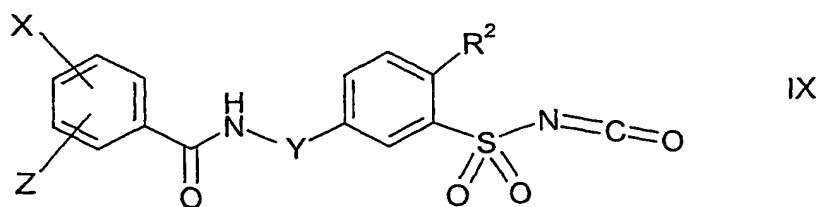
hydrogen peroxide, sodium peroxide or nitrous acid. Benzenesulfonylthioureas can also be desulfurized by treating them with phosgene or phosphorus pentachloride. As intermediates chloroformic amidines or carbodiimides are obtained which can be converted into the corresponding substituted benzenesulfonylureas by hydrolysis or
 5 the addition of water, for example.

(g) Benzenesulfonylureas of the formula Ia can be prepared from benzenesulfonyl halides of the formula VIII using R^1 -substituted ureas or R^1 -substituted bis(trialkylsilyl)ureas. Standard methods can be used to remove the trialkylsilyl
 10 protecting group from the primarily resulting (trialkylsilyl)benzenesulfonylureas. Furthermore, the sulfonyl chlorides of the formula VIII can be reacted with parabanic acids to give benzenesulfonylparabanic acids, whose hydrolysis with mineral acids yields the corresponding benzenesulfonylureas of the formula Ia.

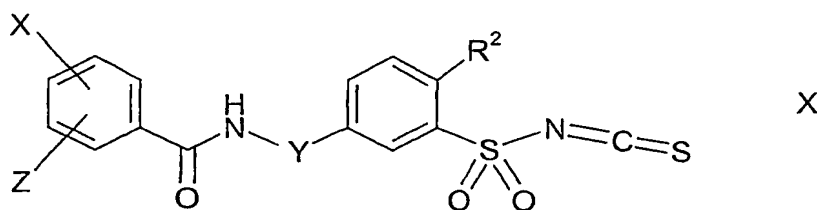


15

(h) Benzenesulfonylureas of the formula Ia can be prepared by reacting amines of the formula R^1-NH_2 with benzenesulfonyl isocyanates of the formula IX. In the same way, amines of the formula R^1-NH_2 can be reacted with benzenesulfonylcarbamic
 20 esters, with benzenesulfonylcarbamoil halides or with benzenesulfonylureas of the formula Ia in which R^1 is hydrogen, to give compounds of the formula Ia.



(i) Benzenesulfonylthioureas of the formula Ib can be prepared by reacting amines of the formula R^1-NH_2 with benzenesulfonyl isothiocyanates of the formula X. In the same way, amines of the formula R^1-NH_2 can be reacted with benzenesulfonylcarbamic thioesters or benzenesulfonylcarbamoyl thiohalides to give compounds of the formula Ib.

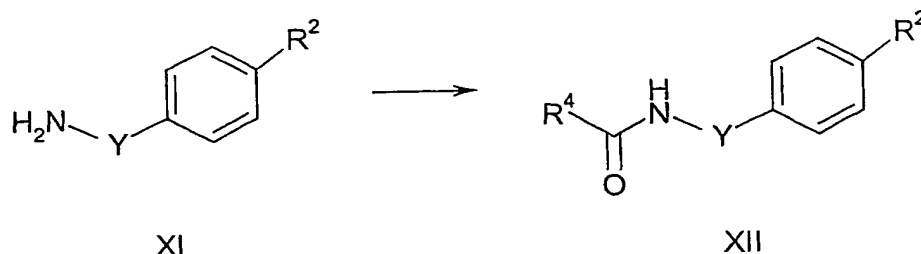


(k) Correspondingly substituted benzenesulfonylureas or benzenesulfinylureas can be oxidized to give benzenesulfonylureas of the formula Ia using oxidizing agents such as hydrogen peroxide, sodium peroxide or nitrous acid.

The starting compounds for the abovementioned processes for synthesizing the compounds of the formula I can be prepared using methods which are known per se and are described in the literature (for example in the standard works such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; or in the abovementioned patent specifications), under reaction conditions which are known and suitable for said reactions. It is also possible to make use of variants which are known per se but which are not mentioned here in detail. If desired, the starting compounds can also be formed in situ such that they are not isolated from the reaction mixture but are immediately subjected to further reaction.

Suitably substituted amines of the formula XI can be acylated and subjected to a halosulfonation. R^2 and Y in formula XI have the meanings mentioned above with respect to formula I, however, in addition R^2 in formula XI can also be a precursor of one of the abovementioned groups, which precursor is then converted, in one or more subsequent steps, into the final R^2 group. Suitable acylating agents R^4-COB for

acylating the amino group in the compounds of the formula XI are alkyl esters, halides (for example chlorides or bromides) or anhydrides of carboxylic acids.

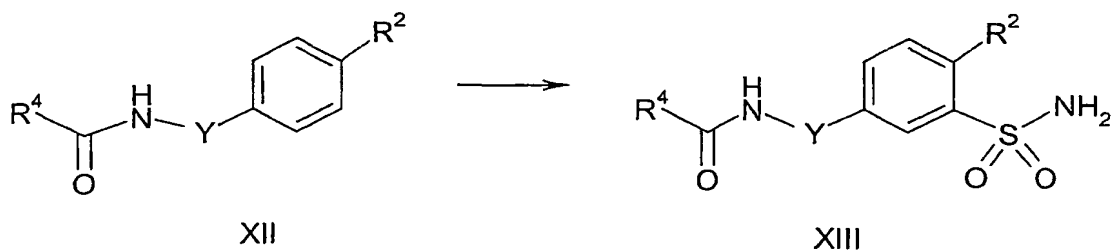


5

R^4 is, for example, a trihalomethyl residue, a $(\text{C}_1\text{-C}_4)$ -alkyl residue or a phenyl residue. If R^4 is a phenyl residue, the compound of the formula $\text{R}^4\text{-COB}$ is a benzoic acid derivative. The benzoic acid derivative can be unsubstituted or substituted, for example by one or two identical or different residues such as X and Z, with X and Z
 10 being defined as above with respect to formula I. Thus, X can be hydrogen, $(\text{C}_1\text{-C}_6)$ -alkyl or halogen, and Z can be halogen, $(\text{C}_1\text{-C}_4)$ -alkyl, fluoro- $(\text{C}_1\text{-C}_4)$ -alkyl-, $(\text{C}_1\text{-C}_4)$ -alkoxy or fluoro- $(\text{C}_1\text{-C}_4)$ -alkoxy-. The group B is a leaving group, such as halogen, $(\text{C}_1\text{-C}_4)$ -alkoxy, trihaloacetoxy or $(\text{C}_1\text{-C}_4)$ -alkylcarbonyloxy, for example. Examples of
 15 compounds of the formula $\text{R}^4\text{-COB}$ are acetic anhydride, trihaloacetic anhydride, such as trifluoroacetic anhydride, acetyl halides, trihaloacetyl halides, propionyl chloride, isobutyryl bromide, isobutyryl chloride, formic/acetic anhydride, benzoyl chloride and substituted benzoic acid derivatives such as 5-chloro-2-methoxybenzoyl
 20 chloride, 5-chloro-2-methoxybenzoic anhydride, $(\text{C}_1\text{-C}_4)$ -alkyl 5-chloro-2-methoxybenzoate, 5-tert-butyl-2-methoxybenzoyl chloride or 2,5-difluorobenzoyl chloride. The syntheses of the compound of the formula XII are preferably carried out in the presence of a tertiary amine base, such as pyridine or a trialkylamine, in the
 presence or absence of an inert solvent, it also being possible for a catalyst such as dimethylaminopyridine to be present. In general, the reaction is carried out at
 25 temperatures of from about 0°C to about 160°C , preferably from about 20°C to about 150°C . The acyl group in the compound of the formula XII can be either a protecting group or, in the case of the benzoic acid derivatives, a part of the final compound of the formula I. Examples of suitable inert solvents for the acylation are ethers, such as

tetrahydrofuran, dioxane, or glycol ethers, such as ethylene glycol monomethyl ether or ethylene glycol monoethyl ether (methyl glycol or ethyl glycol) or ethylene glycol dimethyl ether, ketones, such as acetone or butanone, nitriles, such as acetonitrile, nitro compounds, such as nitromethane, esters, such as ethyl acetate, amides, such as DMF or NMP, hexamethylphosphoric triamide, sulfoxides, such as DMSO, chlorinated hydrocarbons, such as dichloromethane, chloroform, trichloroethylene, 1,2-dichloroethane or carbon tetrachloride, or hydrocarbons, such as benzene, toluene or xylenes. Mixtures of these solvents with one another are also suitable.

- 10 The sulfonamides of the formula XIII can be prepared from the compounds of the formula XII using methods which are known per se, employing reaction conditions



- 15 which are known and suitable for such reactions. It is also possible to make use of variants which are known per se but which are not mentioned here in detail. If desired, the syntheses can be carried out in one, two or more steps. In particular, preference is given to processes in which the acylated amine of the formula XII is converted, using electrophilic reagents, in the presence or absence of inert solvents at temperatures of from about -10°C to about 120°C, preferably from 0°C to about 100°C, into aromatic sulfonic acids or their derivatives, such as sulfonyl halides. For example, it is possible to carry out sulfonations using sulfuric acids or fuming sulfuric acid, halosulfonations using halosulfonic acids, reactions with sulfonyl halides in the presence of anhydrous metal halides, or reactions with thionyl halides in the presence of anhydrous metal halides with a subsequent oxidation carried out in a known manner to give aromatic sulfonyl chlorides. If sulfonic acids are the primary reaction products, these can then be either converted directly, or after treatment with

tertiary amines, such as pyridine or trialkylamines, or with alkali metal or alkaline earth metal hydroxides or reagents which form these basic compounds in situ, in a known manner into sulfonyl halides, using acid halides such as phosphorus trihalides, phosphorus pentahalides, phosphorus oxychlorides, thionyl halides or oxalyl halides. The sulfonic acid derivatives can be converted into sulfonamides in a manner known from the literature. Preference is given to reacting the sulfonyl chlorides, in an inert solvent and at temperatures of from about 0°C to about 100°C, with aqueous ammonia in the absence or presence of an organic solvent. It is furthermore possible to synthesize aromatic sulfonamides, in accordance with methods which are described in the literature, from the acylated amines of the formula XII by means of reaction with alkali metal-organic or alkaline earth metal-organic reagents, in an inert solvent under an inert gas atmosphere at temperatures of from about -100°C to about 50°C, preferably of from about -100°C to about 30°C, and with sulfur dioxide and subsequent thermal treatment with sulfamic acid.

15

If the group R^2 in the compound of the formula XIII is a precursor of the final R^2 group, the conversion of the group R^2 can be effected either before or after introducing the sulfamoyl group SO_2NH_2 . If it is effected after introducing the sulfamoyl group, it may be appropriate, when converting the R^2 group, to use a standard method to protect the sulfamoyl group reversibly, for example by converting it into the N,N-dimethylaminomethylenesulfamoyl group by reaction with a dimethylformamide acetal.

If the acyl group in the compound of the formula XIII functions as a protecting group for the amino group, this protecting group can then be eliminated, after the sulfonamide group has been introduced, by treating with acids or bases. By treatment with aqueous acids or with acids in inert solvents the acid addition salt of the amino compound can be formed. Sulfuric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or organic acids, for example, are suitable for carrying out this protecting group elimination. The elimination of the amino protecting group in the compound of the formula XIII using bases can be effected in aqueous or inert solvents. Examples of

suitable bases are alkali metal or alkaline earth metal hydroxides, such as sodium hydroxide, potassium hydroxide or calcium hydroxide, or alkali metal or alkaline earth metal alcoholates, such as sodium methoxide, sodium ethoxide, potassium methoxide or potassium ethoxide. The benzenesulfonamides of the formula III can be prepared from the sulfonamide-substituted amines, or their acid addition salts, which have been prepared in this way, by acylation with substituted benzoic acids or benzoic acid derivatives, as explained above for the acylation of the compounds of the formula XI.

- 10 The compounds of the formula I can possess one or more chiral centers. When they are prepared, they can be obtained as racemates or, if optically active starting compounds are used, also in optically active form. If the compounds possess two or more chiral centers, they can then accrue, during the synthesis, as mixtures of racemates the individuals of which can be isolated in pure form, for example, by
- 15 recrystallizing from inert solvents. If desired, racemates which have been obtained can be separated into their enantiomers using methods which are known per se. For example, diastereomers can be formed from the racemate by reaction with an optically active resolving agent. Examples of suitable resolving agents for basic compounds are optically active acids such as the R or the R,R or the S or the S,S
- 20 form of tartaric acid, dibenzoyltartaric acid, diacetyltartaric acid, camphorsulfonic acids, mandelic acids, malic acid or lactic acid. The diastereomers can be separated in a manner known per se, for example by fractional crystallization, and the enantiomers can then be liberated from the diastereomers in a manner known per se. It is furthermore possible to effect a separation of the enantiomers by means of
- 25 chromatography on optically active support materials.

Depending on the nature of the residues R^1 , R^2 , R^3 , E, X, Y and Z, in some cases a process from those described above for preparing the compounds of the formula I will be unsuitable, or will it become necessary to take precautions for protecting

30 active groups, for example. Such cases which occur relatively rarely, can be easily recognised by the skilled person, and no difficulty is involved in successfully using another of the above-described synthesis processes in such cases. Furthermore,

with regard to the preparation of the compounds of the formula I which are to be used according to the invention, reference is made to US-A-5574069 (EP-A-612724) and US-A-5652268 (EP-A-727416).

- 5 The suitability of the compounds of the formula I for treating pathological changes in blood pressure associated with septic shock or occurring in the generalized inflammatory syndrome (SIRS) state can be established, for example, in the pharmacological model in the pig which is described further below (endotoxin model, synonym: LPS model (LPS = lipopolysaccharide)). The effect can also be examined,
10 for example, in rats, mice, cats, guinea pigs, rabbits, dogs or monkeys.

Due to the biological activity which has been found, the compounds of the formula I and their physiologically tolerated salts can be used in animals, preferably in mammals, and in particular in humans, as medicaments on their own, in mixtures
15 with one another, for example as a mixture of two compounds of the formula I and/or their physiologically tolerated salts, or together with other pharmacologically active compounds, in the treatment of septic shock or the generalized inflammatory syndrome (SIRS), in particular for treating pathological changes in blood pressure associated with septic shock or occurring in the generalized inflammatory syndrome
20 (SIRS) state. Preferably the compounds of the formula I and their physiologically tolerated salts are used for this purpose in the form of pharmaceutical preparations (or pharmaceutical compositions). The present invention also relates to a method for treating septic shock or the generalized inflammatory syndrome (SIRS), in particular a method for treating pathological changes in blood pressure associated with septic
25 shock or occurring in the generalized inflammatory syndrome (SIRS) state, in which method an effective dose of one or more compounds of the formula I and/or their physiologically tolerated salts is/are administered to a human or an animal. The invention furthermore relates to pharmaceutical preparations (or pharmaceutical compositions) for treating septic shock or the generalized inflammatory syndrome
30 (SIRS), in particular pharmaceutical preparations for treating pathological changes in blood pressure associated with septic shock or occurring in the generalized inflammatory syndrome (SIRS) state, which preparations comprise an effective dose

of one or more compounds of the formula I and/or their physiologically tolerated salts together with a pharmaceutically acceptable carrier, i.e. one or more pharmaceutically acceptable vehicles or carrier substances and/or auxiliary substances or additives.

5

Medicaments which are to be used according to the invention and which comprise the compounds of the formula I and/or their physiologically tolerated salts, can be administered enterally, for example orally or rectally, for example in the form of pills, tablets, film tablets, sugar-coated tablets, granules, hard gelatin capsules, soft gelatin capsules, suppositories, solutions, such as aqueous, alcoholic or oily solutions, juices, drops, syrups, emulsions or suspensions. The medicaments can also be administered parenterally, for example subcutaneously, intramuscularly or intravenously, in the form of injection solutions or infusion solutions. Other examples of suitable forms of administration are percutaneous or topical administration, for example in the form of ointments, creams, pastes, lotions, gels, sprays, powders, foams, aerosols or solutions, or use in the form of implants. In the use according to the present invention it is particularly suitable to use the compounds of the formula I and/or their physiologically tolerated salts, or the medicaments comprising them, by injection or infusion. Preferred forms of medicaments according to the invention thus include injection solutions and infusion solutions and pharmaceutical preparations from which injection solutions and infusion solutions are obtained, for example by adding a liquid carrier substance.

The pharmaceutical preparations to be employed according to the invention can be produced using the known standard methods for producing pharmaceutical preparations. For this, one or more compounds of the formula I and/or their physiologically tolerated salts is/are mixed together with one or more solid or liquid galenic carrier substances and/or additives or auxiliary substances and, if a combination preparation is desired, additional pharmaceutically active ingredients having a therapeutic or prophylactic effect, and brought into a suitable administration form or dosage form which can then be used as a medicament in human medicine or veterinary medicine. The pharmaceutical preparations comprise a therapeutically or

prophylactically effective dose of the compounds of the formula I and/or their physiologically tolerated salts which normally amounts to from about 0.5 to about 90 per cent by weight of the pharmaceutical preparation. While the quantity of active compound of the formula I and/or its physiologically tolerated salts in the
5 pharmaceutical preparations is normally from about 0.2 mg to about 1000 mg, preferably from about 1 mg to about 500 mg, per dose unit, it can also be higher depending on the nature of the pharmaceutical preparation.

Suitable carrier substances for producing pharmaceutical preparations are organic or
10 inorganic substances which are suitable, for example, for enteral (for example oral) or parenteral (for example intravenous) administration or topical uses and which do not react with the active compounds in an undesirable manner, for example water, saline, vegetable oils, alcohols, such as ethanol, isopropanol or benzyl alcohols, 1,2-propanediol, polyethylene glycols, dimethylacetamide, glyceryl triacetate, gelatin,
15 carbohydrates such as lactose or starch, talc, lanolin or vaseline. It is also possible to use mixtures of two or more carrier substances, for example mixtures of two or more solvents, in particular mixtures of one or more organic solvents with water. Additives or auxiliary substances which can be present in the pharmaceutical preparations include stabilizing agents, wetting agents, emulsifiers, solubilizers, thickeners, salts,
20 for example for influencing the osmotic pressure, glidants, preservatives, dyes, flavorings, aromatizing substances and/or buffering substances, such as, for example stearic acid, magnesium stearate, polyvinylpyrrolidone, sodium chloride, silica, cellulose derivatives, etc. The pharmaceutical preparations can also comprise one or more additional active ingredients, for example vitamins or protein C activators. The
25 compounds of the formula I and/or their physiologically tolerated salts can also be lyophilized and the resulting lyophilisates can, for example, be used for producing injection preparations and infusion preparations. Liposomal preparations are also suitable, for example for topical use.

30 The dose of the active compound of the formula I and/or of one of its physiologically tolerated salts which is to be administered in the use according to the invention depends on the individual case and, as usual, has to be adapted to the individual

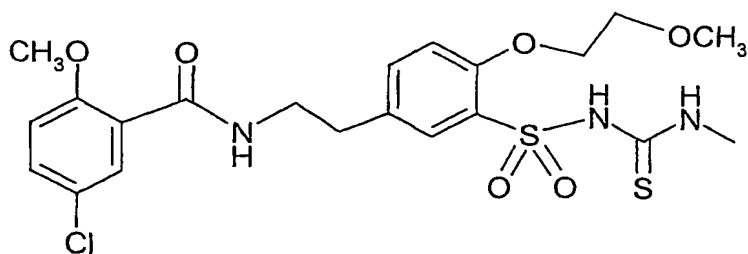
circumstances in order to achieve an optimal effect. Thus, it depends on the circumstances of the specific case, on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the strength and duration of effect of the compounds employed, on whether the therapy or prophylaxis is being conducted acutely or over a relatively long period of time, or on whether other active compounds, in addition to compounds of the formula I, are being administered. In general, a dose range for treating septic shock, sepsis or generalized inflammatory syndrome (SIRS) in humans of from about 0.1 mg to about 100 mg per kg and day is appropriate for achieving the intended effect when the dose is being administered to an adult weighing about 75 kg. Preference is given to a dose range of from about 1 mg to about 30 mg per kg and day (in each case mg per kg of body weight). The daily dose can be administered as one single dose or be subdivided into several individual doses, for example one, two, three or four individual doses. The dose can, for example, be administered as a bolus or continuously, for example by means of infusion or continuous infusion. Where appropriate, it may be necessary to deviate upwards or downwards from the abovementioned daily dose depending on the individual response.

Examples

20

Example 1

1-(5-(2-(5-Chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)phenylsulfonyl)-3-methylthiourea



25

670 mg of 5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)-benzenesulfonamide were dissolved in 10 ml of absolute dimethylformamide and 70 mg of 60% sodium hydride were added. The mixture was stirred at room temperature for 20 min and 1.6 ml of a 1M solution of methyl isothiocyanate in dimethylformamide were then added dropwise. The mixture was heated at 80°C for 1.5 h. After it had been cooled down, the mixture was added dropwise to 100 ml of 1N hydrochloric acid. The resulting mixture was then extracted with ethyl acetate, the organic phase was separated off and dried and the solvent removed in vacuo. The resulting solid was dissolved in a little hot ethanol and precipitated with water. Yield 720 mg. Melting point 134 °C.

Preparation of 5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)-benzenesulfonamide

a) 4-(2-Trifluoroacetamidoethyl)-2-(N,N-dimethylaminomethyleneaminosulfonyl)-anisole
32.6 g (100 mmol) of 2,2,2-trifluoro-N-(2-(4-methoxy-3-sulfamoylphenyl)ethyl)-acetamide (obtainable from 2-(4-methoxyphenyl)ethylamine by conversion into the trifluoroacetamide, reaction with chlorosulfonic acid and reaction with ammonia) were dissolved in 70 ml of dimethylformamide and 16 ml (120 mmol) of N,N-dimethylformamide dimethyl acetal were added. The mixture was stirred for 3 h at room temperature and poured onto ice/NaHSO₄ solution (5%). The precipitate was filtered off with suction, washed with water and dried. 32.5 g (85%) of the title compound were obtained as a white solid. Melting point: 143-144°C. MS (ESI) m/e 382 (M+H⁺).

b) 4-(2-Trifluoroacetamidoethyl)-2-(N,N-dimethylaminomethyleneaminosulfonyl)-phenol hydrobromide
32.5 g (85 mmol) of the compound of step a) were dissolved in 450 ml of dichloromethane and 100 ml (100 mmol) of a 1M solution of boron tribromide in dichloromethane were added slowly. The mixture was stirred at room temperature for 5 h, treated with 150 ml of methanol and poured onto 2 l of diisopropyl ether. The

precipitate was filtered off. Yield: 36.0 g (95%) of the title compound as a colorless solid. Melting point: 160-161°C. MS (ESI) m/e 368 (M+H⁺).

c) 2-(4-(2-Methoxyethoxy)-3-sulfamoylphenyl)ethylamine hydrochloride

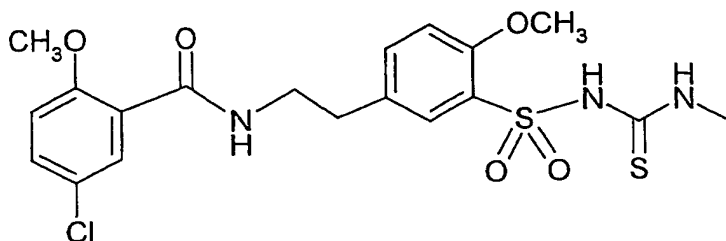
- 5 2.7 g (6 mmol) of the compound of step b), 2.92 g (21 mmol) of 2-bromoethyl methyl ether and 2.1 g (15 mmol) of potassium carbonate were stirred in 100 ml of dimethylformamide for 3 h at 70°C. The mixture was then diluted with ethyl acetate, washed with aqueous sodium chloride solution, and the organic phase was dried and concentrated in vacuo. 1.9 g (85%) of the intermediate were obtained by
- 10 chromatographing the residue with ethyl acetate. The intermediate was then heated under reflux for 8 h in a mixture of 25 ml of methanol and 25 ml of 5.5 N hydrochloric acid. The mixture was concentrated, the residue was washed with ethanol; and the precipitate was filtered off with suction and washed with ethanol. 1.2 g (83%) of the title compound were obtained as a colorless solid. Melting point: 195-197°C. MS
- 15 (ESI) m/e 275 (M+H⁺).

d) 5-(2-(5-Chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)-benzenesulfonamide

- 0.75 g (3.65 mmol) of 5-chloro-2-methoxybenzoyl chloride were added to a solution
- 20 of 1.1 g (3.5 mmol) of the compound of step c) and 1 ml of triethylamine in 20 ml of dry tetrahydrofuran and the reaction mixture was stirred at room temperature for 1.5 h. 80 ml of water were then added, and the precipitated product was filtered off, washed with water and dried in vacuo. Yield: 1.32 g (85%).

25 Example 2

1-(5-(2-(5-Chloro-2-methoxybenzamido)ethyl)-2-methoxyphenylsulfonyl)-3-methylthiourea



400 mg of 5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-methoxybenzenesulfonamide were dissolved in 5 ml of absolute dimethylformamide and 42 mg of 60% sodium hydride were added. The mixture was stirred at room temperature for 30 min. 1.2 ml of a 1M solution of methyl isothiocyanate in dimethylformamide were then added dropwise and the mixture was heated at 80°C for 1.5 h. After it had been cooled down, the reaction mixture was added dropwise to 50 ml of 1N hydrochloric acid. The precipitated product was filtered off with suction and dried. Yield 96%. Melting point 190-193°C.

Example 3

Aqueous solution for intravenous administration

In order to prepare 10 ml of a solution for intravenous application which contains 10 mg of active compound per ml, 100 mg of the sodium salt of 1-(5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)phenylsulfonyl)-3-methylthiourea were dissolved in 10 ml of isotonic (0.9%) sodium chloride solution.

Pharmacological investigations

20

Anesthetized pigs were infused continuously with lipopolysaccharide (LPS) (0.15 µg/kg/h; n = 7). This led to a decrease in the peripheral resistance. After 3.9 hours, 1-(5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)phenylsulfonyl)-3-methylthiourea sodium salt was administered at a dose of 5 - 10 mg/kg (intravenously; aqueous solution). As a result, the peripheral mean arterial blood pressure rose significantly by 19.6 ± 3.2 mm Hg ($p < 0.001$). The peripheral resistance, which under the effect of the endotoxin had fallen to $60.8 \pm$

4.1% of the starting value that had been present prior to administering the endotoxin, rose to $80.8 \pm 5.1\%$ of the starting value that had been present prior to administering the endotoxin ($p < 0.0001$).

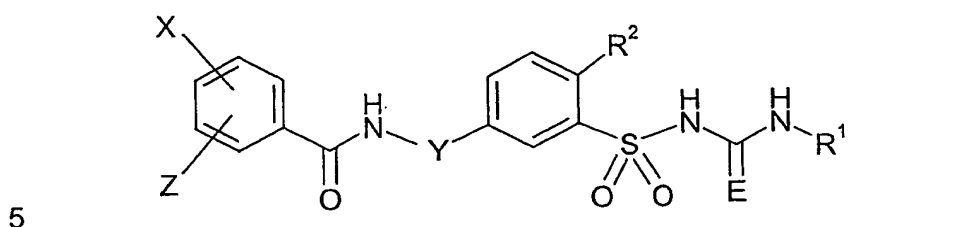
- 5 When the 1-(5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)-phenylsulfonyl)-3-methylthiourea sodium salt was administered as an infusion (total dose 5 - 10 mg/kg), a marked improvement was already seen after a dose of 1 - 2.5 mg/kg had been infused.
- 10 In another experimental approach performed on anesthetized pigs, 1 $\mu\text{g/kg}$ of LPS was administered as a bolus ($n = 5$). This led, within 15 - 20 min, to a dangerous increase in the systolic pulmonary arterial pressure from 30.6 ± 0.7 mm Hg to 67.2 ± 6.0 mm Hg. Administration of 5 mg/kg of 1-(5-(2-(5-chloro-2-methoxybenzamido)ethyl)-2-(2-methoxyethoxy)phenylsulfonyl)-3-methylthiourea
- 15 sodium salt (intravenously; bolus) lowered the systolic pulmonary arterial pressure significantly to 46.6 ± 4.0 mm Hg ($p < 0.01$).

These experimental data prove that in septic shock and in the generalized inflammatory syndrome (SIRS) state the compounds of the formula I raise the

20 peripheral arterial blood pressure and at the same time lower the increased pulmonary arterial pressure, and demonstrate the superiority of the compounds of the formula I, as compared with other vasoconstrictive substances, in the treatment of septic shock.

Patent claims

1. The use of a benzenesulfonyl(thio)urea of the formula I,



in which

R¹ is hydrogen, (C₁-C₈)-alkyl, (C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkyl-(C₁-C₄)-alkyl- or fluoro-(C₁-C₈)-alkyl-;

10 R² is (C₁-C₆)-alkoxy, (C₃-C₈)-cycloalkyloxy, (C₃-C₈)-cycloalkyl-(C₁-C₄)-alkoxy-, (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy- or (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy-(C₁-C₄)-alkoxy-;

E is oxygen or sulfur;

Y is a hydrocarbon residue of the formula -(CR³₂)_n-, in which the residues R³, all independently of each other, are hydrogen or (C₁-C₂)-alkyl, and n is 1, 2, 3 or 4;

15 X is hydrogen, halogen or (C₁-C₆)-alkyl;

Z is halogen, (C₁-C₄)-alkyl, fluoro-(C₁-C₄)-alkyl-, (C₁-C₄)-alkoxy or fluoro-(C₁-C₄)-alkoxy-;

in all its stereoisomeric forms and mixtures thereof in all ratios, and/or its

physiologically tolerated salts, for producing a medicament for treating septic shock

20 or the generalized inflammatory syndrome (SIRS).

2. The use as claimed in claim 1 for producing a medicament for treating pathological changes in blood pressure in septic shock or in the generalized inflammatory syndrome (SIRS) state.

25

3. The use as claimed in claims 1 and/or 2, wherein, in the formula I,

R¹ is hydrogen or (C₁-C₆)-alkyl;

R^2 is (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy- or (C₁-C₆)-alkoxy-(C₁-C₄)-alkoxy-(C₁-C₄)-alkoxy-;

E is oxygen or sulfur;

Y is a hydrocarbon residue of the formula $-(CR^3)_n-$, in which the residues R^3 , all
5 independently of each other, are hydrogen or (C₁-C₂)-alkyl, and n is 1, 2, 3 or 4;

X is hydrogen, halogen or (C₁-C₄)-alkyl;

Z is halogen, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy.

4. The use as claimed in one or more of claims 1 to 3, wherein, in the formula I,

10 R^1 is (C₁-C₄)-alkyl;

R^2 is methoxy or 2-methoxy-ethoxy-;

E is oxygen or sulfur;

Y is the hydrocarbon residue of the formula $-(CR^3)_n-$, in which the residues R^3 all are
hydrogen, and n is 2;

15 X is chlorine, fluorine or (C₁-C₃)-alkyl;

Z is chlorine, fluorine, (C₁-C₃)-alkyl or (C₁-C₃)-alkoxy.

5. The use as claimed in one or more of claims 1 to 4, wherein 1-(5-(2-(5-chloro-2-
methoxybenzamido)ethyl)-2-(2-methoxyethoxy)phenylsulfonyl)-3-methylthiourea

20 and/or a physiologically tolerated salt thereof is/are employed.

6. The use as claimed in one or more of claims 1 to 4, wherein 1-(5-(2-(5-chloro-2-
methoxybenzamido)ethyl)-2-methoxyphenylsulfonyl)-3-methylthiourea and/or a
physiologically tolerated salt thereof is/are employed.

25

7. The use as claimed in one or more of claims 1 to 6, wherein the medicament
comprising the compound of the formula I and/or a physiologically tolerated salt
thereof is administered by injection or infusion.

30 8. The use as claimed in one or more of claims 1 to 7, wherein the sodium salt of the
compound of the formula I is employed.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/06538

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/17 A61P31/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 15204 A (AVENTIS PHARMA GMBH) 23 March 2000 (2000-03-23) cited in the application abstract page 3, line 20 -page 4, line 11 claims 1-24	1-8
A	WO 00 75106 A (WISCONSIN ALUMNI RES FOUND) 14 December 2000 (2000-12-14) abstract page 6, line 15 page 8, line 20,21 claims 1-8,12-21	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

21 October 2002

Date of mailing of the international search report

29/10/2002

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Taylor, G.M.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/06538

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 727 416 A (HOECHST AG) 21 August 1996 (1996-08-21) cited in the application abstract page 2, line 1 -page 3, line 23 claims 1-12	1-8
A	EP 0 612 724 A (HOECHST AG) 31 August 1994 (1994-08-31) cited in the application abstract page 1, line 1 -page 4, line 17 claims 1-13	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/06538

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0015204	A	23-03-2000	DE 19841534 A1	16-03-2000
			DE 19901061 A1	20-07-2000
			AU 5744499 A	03-04-2000
			BR 9913572 A	22-05-2001
			CA 2343009 A1	23-03-2000
			CN 1319014 T	24-10-2001
			WO 0015204 A2	23-03-2000
			EP 1117409 A2	25-07-2001
			HU 0103534 A2	29-05-2002
			JP 2002524497 T	06-08-2002
			NO 20011117 A	02-05-2001
			PL 347215 A1	25-03-2002
			TR 200100692 T2	23-07-2001
			US 2002082300 A1	27-06-2002
WO 0075106	A	14-12-2000	US 6294694 B1	25-09-2001
			AU 3929600 A	28-12-2000
			WO 0075106 A2	14-12-2000
			US 2002032347 A1	14-03-2002
EP 0727416	A	21-08-1996	DE 19505397 A1	22-08-1996
			AT 189213 T	15-02-2000
			AU 700793 B2	14-01-1999
			AU 4556096 A	29-08-1996
			BR 9600778 A	23-12-1997
			CA 2169694 A1	18-08-1996
			CN 1134414 A ,B	30-10-1996
			CZ 9600436 A3	11-09-1996
			DE 59604262 D1	02-03-2000
			DK 727416 T3	13-06-2000
			EP 0727416 A1	21-08-1996
			ES 2143675 T3	16-05-2000
			FI 960689 A	18-08-1996
			GR 3033049 T3	31-08-2000
			HK 1011965 A1	27-10-2000
			HR 960077 A1	31-12-1997
			HU 73973 A2	28-10-1996
			IL 117150 A	19-03-2001
			JP 8245554 A	24-09-1996
			NO 960627 A	19-08-1996
			NZ 280991 A	29-01-1997
			PL 312528 A1	19-08-1996
			PT 727416 T	30-06-2000
			SI 9600049 A ,B	31-10-1996
			SK 21196 A3	01-10-1996
			TR 960831 A2	21-10-1996
			US 5652268 A	29-07-1997
			ZA 9601231 A	27-08-1996
EP 0612724	A	31-08-1994	AT 146775 T	15-01-1997
			AU 664940 B2	07-12-1995
			AU 5527994 A	01-09-1994
			CA 2116165 A1	24-08-1994
			CY 2034 A	20-02-1998
			DE 59401361 D1	06-02-1997
			DK 612724 T3	16-06-1997
			EP 0612724 A1	31-08-1994
			ES 2098069 T3	16-04-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/06538

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0612724	A	FI 940810 A	24-08-1994
		GR 3022550 T3	31-05-1997
		HK 1006166 A1	12-02-1999
		HU 71104 A2	28-11-1995
		JP 2778450 B2	23-07-1998
		JP 7304728 A	21-11-1995
		NO 940600 A	24-08-1994
		NZ 250925 A	26-09-1995
		PL 302325 A1	05-09-1994
		PL 179268 B1	31-08-2000
		TW 429245 B	11-04-2001
		US 6090981 A	18-07-2000
		US 5574069 A	12-11-1996
		US 6335467 B1	01-01-2002
		US 5698596 A	16-12-1997
		US 5776980 A	07-07-1998
		US 2002058838 A1	16-05-2002

THIS PAGE BLANK (USPTO)